Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

By the above amendments, new claim 47 is introduced. This new claim finds descriptive support in pending claim 1, but also specifies in the "treating" step that the one or more non-predominate target-binding ligands are not reduced in concentration or eliminated from the first pool as are the one or more predominate target-binding ligands. Descriptive support for this limitation appears in the description of the invention at pages 12-14 and Figure 1 of the present application. Therefore, no new matter has been introduced by new claim 47.

Claims 1-15, 18-22, and 47 remain pending. No excess claim fees are required with this submission.

Applicants would like to thank Examiner Thomas for the courtesy extended to the undersigned representative during the telephone interview held on March 7, 2008. The substance of the interview is summarized below in the discussion of the bases of rejection.

The rejection of claims 1, 2, 4, 7-11, and 14 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,792,613 to Schmidt et al. ("Schmidt") is respectfully traversed.

Schmidt teaches a method for selecting an RNA aptamer that binds a nucleic acid molecule by way of shape recognition. According to this method, a large, random RNA population is pretreated with a sufficient quantity of blocking oligodeoxynucleotide to preclude potential Watson-Crick base pairing interactions between RNA molecules in the population and the selecting (or target) nucleic acid molecule. After pretreatment, the candidate RNA population is subjected to a selection process whereby it is first contacted with the selecting nucleic acid molecule to allow non-covalent binding of the RNA aptamer to the structural element of the selecting nucleic acid molecule. The resulting RNA aptamer:nucleic acid molecule complex is then separated from the remaining free RNA molecules, after which the complex is dissociated. The selected RNA population is thereby enriched for RNA aptamers that bind the selecting nucleic acid molecule by way of shape recognition. Successive rounds of selection are carried out until at least one characteristic sequence motif becomes apparent, that is, until one specific aptamer sequence or a family of aptamers dominates the pool of selected aptamers. After each round of selection, the selected RNA population, enriched for the RNA aptamer of interest, is preferably reverse transcribed to cDNA, amplified, then transcribed into RNA before beginning the next round of selection.

As discussed during the interview, this is a modified form of the SELEX procedure that uses a blocking oligonucleotide to prevent any RNA ligands that would otherwise bind to the target nucleic acid molecule via Watson-Crick base-pairing from being selected and amplified during the multiple rounds of selection and amplification that is SELEX.

As asserted in applicants' last response and during the above-noted interview, the presently claimed invention covers a process that begins where the modified SELEX process of Schmidt ends (i.e., with an enriched pool of RNA that contains a predominant RNA aptamer species or family). While Schmidt teaches the step of "preparing" as recited in claim 1, Schmidt does not teach the "treating" step (or any subsequent steps) recited in claim 1.

The PTO, at pages 3-4 of the outstanding office action, repeatedly cites the discussion in Schmidt that appears in columns 2-3. However, it is clear in step (c) of Schmidt that this negative selection step results in a by-product that is no longer used by Schmidt; those aptamers that are not selected (because they are bound by the blocking oligonucleotide or simply do not bind the target) are discarded. Moreover, the use of a blocking oligonucleotide in Schmidt as a negative selection does not have the affect of deleting predominant species; it simply precludes hybridizing nucleic acids from ever being selected and amplified, i.e., from becoming a predominant species in the enriched aptamer pool.

Schmidt, therefore, is deficient in several respects.

Firstly, to the extent that the use of the blocking oligonucleotide in Schmidt is considered a treatment of a pool of RNA aptamers, such treatment is applied not to an enriched pool (that contains one or more predominant target-binding RNA ligands), but instead to the library of random aptamers that represent the initial population to be screened. Referring to Figure 1 of the present application, the blocking oligonucleotide of Schmidt would be used on the initial population (left side) prior to an otherwise conventional SELEX procedure. Thus, Schmidt fails to teach "treating the first pool" as presently claimed, because the pool treated by Schmidt does not contain RNA ligands that "comprise[] *one or more predominate* target-binding RNA ligands and one or more non-predominate target-binding RNA ligands."

Secondly, the effect of the Schmidt blocking oligonucleotide, as noted above, is entirely different from the claimed treatment. The blocking oligonucleotide precludes certain aptamers from ever predominating an enriched aptamer pool. This is in contrast to the claimed treatment, which is "effective to reduce the concentration or eliminate the presence of the one or more predominant target-binding RNA ligands from the first pool of RNA ligands" (emphasis added).

Finally, because Schmidt fails to teach the claimed treatment, Schmidt cannot teach the subsequent "amplifying" and "identifying" steps as recited.

For all these reasons, Schmidt clearly does not anticipate the method recited in claim 1, or claims 2, 4, 7-11, and 14 dependent thereon. The rejection is improper, and should be withdrawn.

The rejection of claims 1, 2, 4, 7-11, and 14 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,582,981 to Toole et al. ("Toole") is respectfully traversed.

Toole teaches a method to determine an oligonucleotide sequence which binds specifically to a target. This method is basically a modification of the SELEX procedure, whereby the oligomers (of the initial pool) contain portions that permit amplification. The process involves providing a mixture containing the above-described oligomers and incubating the oligomer mixture with the target substance coupled to a support to form complexes between the target and oligomers bound specifically thereto. The unbound members of the oligonucleotide mixture are removed from the support environment and the complexed oligonucleotide(s) are recovered by uncoupling the target substance from the support. The recovered oligonucleotides are amplified, and the recovered and amplified oligonucleotide(s), which had been complexed with the target, are then sequenced.

Thus, Toole merely teaches a modified SELEX procedure that allows for separation of oligonucleotide(s) that bind the target from those that (i) do not bind the target and (ii) those that bind the support (or the support and target together). See Toole at col. 8, lines 21-27. As discussed during the above-noted interview, Toole merely teaches another approach for the "preparing" step of claim 1, but Toole does not teach the "treating" step (or any subsequent steps) recited in claim 1. Toole, therefore, is deficient for the same three reasons noted above with respect to Schmidt.

In addition, applicants would like to point out that the PTO's assertion at page 8 of the office action (concerning the "treating" step) is incorrect. While Toole certainly teaches removing unbound oligonucleotides, the separation of the unbound oligonucleotides from the target-bound oligonucleotides does not constitute the treatment recited in claim 1. The unbound oligonucleotides are, by definition, those that do not bind the substrate-supported target, and they are simply discarded. *See* col. 7, lines 62-67 (e.g., washed from column). It is only target-binding RNA ligands that are amplified during the SELEX process of Toole. The unbound ligands—the ones washed away—would not be amplified and, therefore, could never predominate the resulting enriched pool created by Toole. Hence, the unbound oligonucleotides that the PTO asserts are eliminated from the pool of Toole do not

constitute the "one or more predominate target-binding RNA ligands" that are reduced in concentration or eliminated from the treated pool as recited in claim 1.

For all these reasons, Toole clearly does not anticipate the method recited in claim 1, or claims 2, 4, 7-11, and 14 dependent thereon. The rejection is improper, and should be withdrawn.

The rejection of claims 3, 5, 6, 12, 13, 15, and 18-22 under 35 U.S.C. § 103(a) for obviousness over Schmidt in view of U.S. Patent No. 6,344,321 to Rabin et al. ("Rabin") and U.S. Patent No. 6,544,741 to Mugasimangalam ("Mugasimangalam") is respectfully traversed.

The teaching and deficiencies of Schmidt are recited above.

Rabin is directed to methods for generating nucleic acid ligands to HGF and c-met using the SELEX process for ligand generation. Figure 2 of Rabin illustrates RNaseH cleavage primers used in hybridization truncate SELEX. Basically, RNaseH cleavage primers are used simply to remove the known 5'- and 3'-terminal nucleic acid sequences from the randomized aptamer sequence selected during the SELEX procedure.

Mugasimangalam is cited for RNase H cleavage of specific mRNA species.

On page 14, the PTO asserts that Schmidt teaches sequencing the one or more unwanted target-binding RNA ligands, citing column 3, lines 32-36. Applicants respectfully disagree for several reasons.

Firstly, because Schmidt knows the sequence of the target, Schmidt knows which sequences will be capable of preventing Watson-Crick base pairing of ligands with the target (i.e., an oligo that shares the sequence of the target). The only unwanted target-binding RNA ligands that Schmidt mentions are those that would have bound to the target via Watson-Crick base pairing. Because the blocking oligonucleotide of Schmidt precludes such base pairing from occurring, those unwanted target-binding RNA ligands are not enriched in the enriched aptamer pool of Schmidt. That is, after all, the whole point of Schmidt. In any event, because those unwanted target-binding RNA ligands are not enriched, Schmidt never sequences them. (Schmidt is only interested in sequencing the target-binding ligands that are part of the enriched pool.)

Secondly, Schmidt has no motivation to sequence the unwanted target-binding RNA ligands, because Schmidt gets rid of them via separation of unbound ligands from the desired target-binding ligands. In other words, the unwanted target-binding RNA ligands are simply discarded.

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Finally, Schmidt fails to recognize that the removal of previously sequenced (and identified) target-binding ligands would be useful for identifying other target-binding ligands in the originally enriched pool. Moreover, Schmidt fails to recognize that the substrate itself may act as a target. Thus, Schmidt provides no motivation for removing any subset of enriched target-binding ligands that become unwanted only after they have been sequenced (and presumably screened for binding activity).

Even though Rabin and Mugasimangalam confirm that RNase H treatment was known in the art, persons of skill in the art would not have had any rationale for combining the RNase H treatment of Rabin or Mugasimangalam with the process of Schmidt, because Schmidt provides no basis for removing from the enriched aptamer pool any of the target-binding RNA ligands.

Accordingly, the obviousness rejection of claims 3, 5, 6, 12, 13, 15, and 18-22 is improper and must be withdrawn.

In addition to the foregoing, applicants submit that new claim 47 is patentable for all the reasons noted above as well as the failure of any of the cited references to teach or suggest a "treating" step as recited therein.

Because applicants believe the cited art is deficient in many respects from the claimed invention, applicants respectfully request that the examiner and his supervisor contact the undersigned attorney, if necessary, to further discuss these deficiencies so that this case can be allowed. In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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/Edwin V. Merkel/
Edwin V. Merkel

Registration No. 40,087

NIXON PEABODY LLP 1100 Clinton Square Rochester, New York 14604 Telephone: (585) 263-1128

Facsimile: (585) 263-1600